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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,065	10/12/2007	Tetsuo Mizuno	E1679	5807
8933 7590 10/29/2009 DUANE MORRIS LLP - Philadelphia IP DEPARTMENT 30 SOUTH 17TH STREET PHILADELPHIA, PA 19103-4196			EXAMINER GRASER, JENNIFER E	
			ART UNIT 1645	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/589,065

Applicant(s)

MIZUNO, TETSUO

Examiner

Jennifer E. Graser

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

NOTE: The previous Office Action mailed 2/3/09 is hereby **vacated** in favor of the following Office Action. During a telephone conversation with Applicant's representative, Gary Colby, it was brought to the Examiner's attention that claims 1-48 were actually replaced with claims 1-27/Amended Sheet IPEA/AU in the Article 34 amendment.

Claim Rejections - 35 USC § 112-2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 15-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15, 19, 24 and 25 are vague and indefinite because it is unclear what is encompassed by 'chemical or functional equivalents [of nalidixic acid and rifampicin]'. The structure of these compounds cannot be understood. The metes and bounds of the invention are therefore unclear. Appropriate correction is requested.

Claim 27 provides for the use of the purified culture, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 27 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant claims are drawn to a microorganism which is present within a subject, e.g., the microorganisms was exposed to a microbiostatic substance 'present in, or introduced to, an environment within a subject'. The claims do not recite that the microorganism has been "isolated" and, therefore, reads on a product of nature. A 'therapeutic agent' is an intended use only. The mutations recited in the claims could be found in nature.

Claim Rejections - 35 USC § 112-Deposit Requirement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of the microorganisms recited in the claims. Because it is not clear that the properties of the microorganisms are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the microorganisms, a suitable deposit for patent purposes is required.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

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- 1)The name and address of the depository;
- 2)The name and address of the depositor;
- 3)The date of deposit;
- 4)The identity of the deposit and the accession number given by the depository;
- 5)The date of the viability test;
- 6)The procedures used to obtain a sample if the test is not done by the depository; and
- 7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 112-Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are broadly drawn to any therapeutic agent comprising *any* microorganism which has a reduced capacity to grow and replicate in the presence of

bile salts within a subject to which said microorganism migrates following administration wherein said microorganism is capable of inducing an immune response in said subject, which immune response is directed against an antigen on, or secreted by, the microorganism. Methods of vaccination using these agents and therapeutic agents comprising any *Salmonella* sp. which carries any metabolic-drift mutation resulting in a reduced capacity to grow and replicate in the presence of bile salts are also claimed. These claims are not enabled. The term 'microorganism' in claims 1-3, 9-19, and 24 reads on many structurally distinct organisms, e.g., fungi, viruses, prions, parasites, etc.. The specification does not enable this huge breadth of invention. The specification describes the generation of attenuated bile-sensitive *S.dublin* strains by exposure to a combination of nalidixic acid and rifampicin. Strains which were resistant to naladixic acid and/or rifampicin were identified. Single and double resistant strains were identified. It is not predictable that this teaching would extend to generation of an attenuated strain having sensitivity against microbiostatic agents other than bile, or to any microorganism (including fungi, viruses, prions, etc.) as recited in claims 1-3, 9-19, and 24. Moreover, it is not predictable that any other microbiostatic agent or combination of such agents would induce a metabolic-drift mutation resulting in an attenuated strain having sensitivity to a further microbiostatic agent. There is also no enabling support for the use of any functional or chemical equivalents of nalidixic acid and rifampicin. The instant specification only teaches reduction to practice with live, attenuated strains of *Salmonella dublin*. Tables 10 and 11 identify specific mutations that were found in the strains. However, the results show that many of these strains do

not possess the desired characteristics. Selected mutants N-RM4, N-RM25 and R-NM29 were prepared for the experiments and strain FD436 was also prepared as a control. Figure 11 on page 70 all tested strains showed a prolonged lag phase in their growth cycles in the presence of BS No. 3, albeit to different degrees. Results from the twenty-hour incubation showed that, although the degree of inhibition differed for each strain, the higher the concentration of bile salts the slower the growth rate. After challenge infection, mice suffering from salmonellosis were found in all groups inoculated with FD436 or N-RM4. Clinical signs shown by mice in these groups included low activity, low appetite, dehydration and high respiratory rates, but not abnormal faecal consistency. None of the mice administered N-RM25 or R-NM29 showed signs of salmonellosis throughout the observation period. N-RM25, N-RM4 and R-NM29 were prepared as vaccines and FD436 for challenge infection according to the procedures described previously. Vaccine doses used in the experiments are shown in Tables 31, 32 and 33. In vaccine studies with N-RM25 no clinical symptoms were observed in either vaccinated (Group 1) or control (Group 2) mice before challenge infection. The vaccinated mice did not develop any clinical symptoms following challenge infection. In contrast, all mice except one in the control group developed clinical signs of salmonellosis on Day 2 P.C. All mice in this group were euthanized by Day 5 P.C. due to clinical signs of salmonellosis. The mean time until euthanasia among mice in the control group was 115 h. Therefore, it is clear that the protection from salmonellosis conferred by the vaccine was significant ($p = 0.0079$). See page 106. All mice vaccinated with N-RM4 showed clinical symptoms following vaccination and one of

them died due to acute septicaemia caused by the vaccine strain before challenge infection (Day 8 P.V.). The remaining mice were moderately ill (the mice had shown clinical signs in two or fewer of the five parameters) until Day 12 P.V. then recovered. Only two working embodiments appear to be present in the instant specification, e.g., deposited strains N-RM25 and R-NM29. The specification fails to provide any working examples or results with strains N-RM8, N-RM9, N-RM15, N-RM20 or N-RM27. The results which are present show that the strains performance as a therapeutic agents and its functional characteristics are unpredictable. With the exception of strains N-RM29 and N-RM25, it appears it would take undue experimentation to generate other strains with the claimed characteristics.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-5, 9-22, and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Linde et al. (US Patent 6,136,235).

Linde et al disclose attenuated *Salmonella spp* having Rif and Nal resistance and their use in vaccinating livestock, chickens, and cattle (col. 7, 9). The markers discussed by Applicant are the resistance genes themselves. The attenuated bacteria are prepared by the selection of metabolic drift mutants resistant to Rif and/or Nal prepared from both mutated and wild type bacteria (see Examples and Figures). The

mutants may or may not have another marker. However, the present claims do not exclude other metabolic drift markers. The top of column 3 discloses that the bacteria have sensitivity to bile salts, e.g., reduced capacity to grow and replicate. Claims 1-3, 20, and 22, are drawn to bacteria with intended uses described therein. The limitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A bacteria having the defined mutations as instantly recited would inherently possess the same functional characteristics.

10. Claims 1-5, 9-20, 22, and 24-27 are rejected under 35 U.S.C.102(b) as being anticipated by Bjorkman et al (Proc. Natl. Acad. Sci. 1998. USA, vol. 95, pages 3949-3953).

Bjorkman et al disclose spontaneous rifampicin (Rif), streptomycin (Stm) or nalidixic acid (Nal) resistant *S.typhimurium* mutants (page 123) that may or may not have other identifiable characteristics. It discloses that spontaneous mutants resistant to Rif or Nai in *Salmonella spp* have been mapped to the *rpoB* gene and *gyrA* genes, respectively. The use of these strains as therapeutic agents in methods of vaccination is clearly envisaged (see abstract, Introduction and Discussion). 1-5, 9-20, 22, and 24-27 are drawn to bacteria with intended uses described therein. The limitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the

intended use, then it meets the claim. A bacteria having the defined mutations as instantly recited would inherently possess the same functional characteristics.

11. Claims 1-5, 9-20, 22, 24 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Linde et al (Vet Micro. 1998. Vol. 62: 121-134).

Linde et al discloses live attenuated bacteria produced from metabolic drift mutants prepared from both wild type bacteria (donor) and transduced bacteria (pages 123). They comprise those having Rif or Nal resistance and were found to be attenuated (Tables 2 and 5). They are extracted from fecal samples (page 126) and have a mutation in the Rif or Nal genes. The disclosed bacteria are those presently described and defined are considered to be able to infect stock animals and to colonize and invade the organs as presently defined. Claims 1-5, 9-20, 22, 24 and 25-27 are drawn to bacteria with intended uses described therein. The limitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A bacteria having the defined mutations as instantly recited would inherently possess the same functional characteristics.

12. Claims 1-5, 9-20, 22, and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Blanc-Potard et al (Mol. Gen. Genet. 1995. 247: 680-692).

Blanc-Potard et al teach an isolated, attenuated *S.typhimurium* mutant which is rifampicin resistant (Rif^r). The reference teaches that many of these mutant strains are also resistant to nalidixic acid (Nal). See abstract. In the mutants selected for low-level

resistance to NaI, isolates which harbored mutations genetically linked to the *rpoB* locus were found. One of these mutants was found to be temperature-sensitive for growth. The reference discloses that mutations caused by rifampicin occur exclusively in the Beta subunit, the product of the *rpoB* gene. See second column on page 680, "Introduction". Page 684 teaches the selection of Rif-sensitive *rpoB* mutants with nalidixic acid. The term "therapeutic agent" is an intended use only. Additionally, the functional characteristics recited in the instant claims would be inherent in the bacteria taught by Blanc-Potard which are structurally identical to the bacteria which are claimed. Claims 1-5, 9-20, 22, and 24-27 are drawn to bacteria with intended uses described therein. The limitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A bacteria having the defined mutations as instantly recited would inherently possess the same functional characteristics.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 5-8, 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linde et al. (US Patent 6,136,235), Bjorkman et al (Proc. Natl. Acad.

Sci. 1998. USA, vol. 95, pages 3949-3953) and Linde et al (Vet Micro. 1998. Vol. 62: 121-134) and Blanc-Potard et al (Mol. Gen. Genet. 1995. 247: 680-692), as applied to claims 1-5, 9-20, 27-33, 37-45, 47 and 48 above, in further view of Wray, C. (Irish Vet J. 1993. 46: 137-140) and Smith et al (Am J Vet Res. 1984. 45(11): 2231-2235).

The teachings of Linde et al (USpat), Linde et al (Vet Micro), Bjorkman and Blanc-Potard are set forth above. However, they do not particularly exemplify the use of *S.dublin* as a strain and wherein the *S.dublin* comprises an insertion or deletion in an *rpoB* gene.

Wray et al teach that salmonellosis is predominantly associated with *S.dublin* and *S.typhimurium*. See abstract. Smith et al teach live, attenuated *S.dublin* vaccines. See first page.

The primary references all teach random drift mutations in many different species of *Salmonella*. All of the references teach live attenuated *Salmonella spp* strains having Rif or Nal resistance. Blanc-Potard et al and Bjorkman et al specifically disclose that spontaneous mutants resistant to Rif or Nai in *Salmonella spp* have been mapped to the *rpoB* gene and *gyrA* genes, respectively. The primary references all teach these strains as therapeutic agent/vaccine strains. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that *S.dublin* strains could also be used in a similar manner to the *Salmonella spp* taught in the primary prior art references. The prior art teaches that salmonellosis is primarily associated with *S.dublin* and *S.typhimurium* (see Wray et al). The prior art also teaches the use of live, attenuated strains of *S.dublin* as vaccines were well known (see Smith et al).

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Accordingly, it would have been prima facie obvious for one of ordinary skill in the art to generate attenuated *S.dublin* strains which are Rif and/or Nal sensitive (and, therefore inherently possessing *rpoB* mutations) for use as therapeutic agents in treating salmonellosis as the teachings of Linde et al (USpat), Linde et al (Vet Micro), Bjorkman and Blanc-Portard teach the successful use of such strains in many other species of *Salmonella*.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

10/26/09